

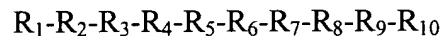
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AMENDMENTS TO THE CLAIMS:

This listing of claims replaces all prior versions, and listings of claims in the application:

WHAT IS CLAIMED IS:

1. (Currently amended) An osteoinductive composition comprising an isolated or recombinant peptide component having the formula:



Formula (I)

~~or a derivative~~ or a pharmaceutically acceptable salt thereof, wherein:

R₁ is H; formyl; mono- or di-lower (C1-C8 linear or branched) alkyl; aryl; lower (C1-C8 linear or branched) alkanoyl; aroyl; aroyl substituted with 1-3 substituents selected from a the group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy; C1-C8 linear or branched alkyloxycarbonyl; aryloxycarbonyl; or aryloxycarbonyl substituted with 1-3 substituents selected from a the group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy;

R₂ and R₈ are each independently selected from D-cysteine, L-cysteine, D-homocysteine, L-homocysteine, D-penicillamine, or L-penicillamine;

R₃, R₄ and R₅ are each glycine; or R₃ and R₄ taken together are δ-amino-pentanoic acid; or R₄ and R₅ taken together are δ-amino-pentanoic acid;

R₆ is arginine or homo-arginine;

R₇ is tryptophan;

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R₉ is glycine; and

R₁₀ is OH, C1-C8 linear or branched alkyl ester, lower aryl ester, or NR₁₁R₁₂ where R₁₁ and R₁₂ are each selected independently from H, C1-C8 linear or branched alkyl, or aryl.

2. (Original) The composition of claim 1, wherein the peptide component has the amino acid sequence of SEQ. ID NO:1.
3. (Original) The composition of claim 2, wherein the peptide component is part of a longer peptide or polypeptide.
4. (Original) The composition of claim 1, wherein said peptide component includes intra-chain disulfide bonds.
5. (Original) The composition of claim 1, wherein said peptide component forms inter-chain disulfide bonds with others of said peptide component.
6. (Original) The composition of claim 5, comprising a homodimer of said peptide component.
7. (Original) The composition of claim 1, further comprising osteoprogenitor stem cells and/or osteoblasts.
8. (Original) The composition of claim 1, further comprising a pharmaceutically acceptable carrier or aqueous solvent.
9. (Original) The composition of claim 1, further including an additive selected from the group consisting of stabilizer, preservative, thickener, solubilizer and combinations thereof.

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10. (Original) The composition of claim 1, further including osteoinductive factors selected from the group consisting of dexamethasone, ascorbic acid-2-phosphate, beta-glycerophosphate, and combinations thereof.

11. (Original) The composition of claim 1, further including an agent selected from the group consisting of antibiotics, antimycotics, anti-inflammatory drugs, immunosuppressive drugs, and combinations thereof.

12. (Original) The composition of claim 1, further including an osteoinductive substance selected from the group consisting of growth factors, cytokines, hormones, enzymes, enzyme inhibitors, bone matrix components, growth differentiation factors and combinations thereof.

13. (Original) The composition of claim 12, wherein the growth factor is selected from the group consisting of epidermal growth factor, platelet-derived growth factor, members of the transforming growth factor superfamily of proteins, insulin-like growth factor, basic fibroblast growth factor, bone morphogenic proteins and combinations thereof.

14. (Original) The composition of claim 1, further comprising a delivery vehicle for said peptide component, said delivery vehicle being a bone-compatible matrix.

15. (Original) The composition of claim 1, further comprising osteoprogenitor stem cells and/or osteoblasts.

16. (Original) The composition of claim 14, wherein said bone-compatible matrix provides for slow release of said peptide component to a patient in need of said composition and/or provides a structure for developing bone in the patient.

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17. (Original) The composition of claim 14, wherein said peptide component is immobilized to, or encapsulated or impregnated within said bone-compatible matrix.

18. (Original) The composition of claim 14, wherein said bone-compatible matrix is a porous structure.

19. (Original) The composition of claim 14, wherein said bone-compatible matrix is in a form selected from the group consisting of powder, microparticles, microspheres, microfibers, microfibrils, strip, gel, web, sponge and combinations thereof.

20. (Original) The composition of claim 14, wherein said bone-compatible matrix is a ceramic.

21. (Original) The composition of claim 20, wherein said ceramic is a three-dimensional scaffold.

22. (Original) The composition of claim 20, wherein said ceramic is selected from the group consisting of calcium sulfate, hydroxyapatite, tricalcium phosphate and combinations thereof.

23. (Original) The composition of claim 14, wherein said bone-compatible matrix is demineralized bone matrix.

24. (Original) The composition of claim 14, wherein said bone-compatible matrix is selected from the group consisting of natural biodegradable polymer, modified natural biodegradable polymer, synthetic biodegradable polymer and combinations thereof.

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25. (Original) The composition of claim 24, wherein said polymer is selected from the group consisting of fibrin, collagen, elastin, celluloses, gelatin, vitronectin, fibronectin, laminin, reconstituted basement membrane matrices, starches, dextrans, alginates, hyaluron, chitin, chitosan, agarose, polysaccharides, hyaluronic acid, poly(lactic acid), poly(glycolic acid), polyethylene glycol, decellularized tissue, self-assembling peptides, polypeptides, glycosaminoglycans, their derivatives and mixtures thereof.

26. (Original) The composition of claim 24, wherein said polymer is selected from the group consisting of polydioxanones, polycarbonates, polyoxalates, poly(α -esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyamides and mixtures and copolymers thereof.

27. (Currently amended) The composition of claim 24, wherein said polymer is selected from the group consisting of stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy) propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, ~~copolymers of polyurethane and (poly(lactic acid))~~, copolymers of polyurethane and poly(lactic acid), copolymers of α -amino acids, copolymers of α -amino acids and caproic acid, copolymers of α -benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof.

28. (Original) The composition of claim 24, wherein said polymer is a synthetic hydrogel polymer.

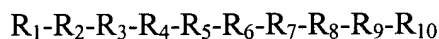
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29. (Original) The composition of claim 24, wherein said peptide component is controllably released from said biodegradable polymer to the site where it is needed by hydrolysis of chemical bonds in said biodegradable polymer.

30. (Currently amended) An osteoinductive implant comprising:

a bone-compatible matrix; and

a peptide component associated with said bone-compatible matrix, the peptide component having the formula:



Formula (I)

~~or a derivative~~ or a pharmaceutically acceptable salt thereof, wherein:

R₁ is H; formyl; mono- or di-lower (C1-C8 linear or branched) alkyl; aryl; lower (C1-C8 linear or branched) alkanoyl; aroyl; aroyl substituted with 1-3 substituents selected from a the group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy; C1-C8 linear or branched alkyloxycarbonyl; aryloxycarbonyl; or aryloxycarbonyl substituted with 1-3 substituents selected from a the group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy;

R₂ and R₈ are each independently selected from D-cysteine, L-cysteine, D-homocysteine, L-homocysteine, D-penicillamine, or L-penicillamine;

R₃, R₄ and R₅ are each glycine; or R₃ and R₄ taken together are δ-amino-pentanoic acid; or R₄ and R₅ taken together are δ-amino-pentanoic acid;

R₆ is arginine or homo-arginine;

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R₇ is tryptophan;

R₉ is glycine; and

R₁₀ is OH, C1-C8 linear or branched alkyl ester, lower aryl ester, or NR₁₁R₁₂ where R₁₁ and R₁₂ are each selected independently from H, C1-C8 linear or branched alkyl, or aryl.

31. (Original) The implant of claim 30, further comprising osteoprogenitor stem cells and/or osteoblasts associated with said bone-compatible matrix.

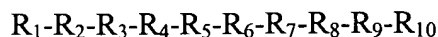
32. (Original) The implant of claim 30, wherein the peptide component has the amino acid sequence of SEQ. ID NO:1.

33. (Original) The implant of claim 30, wherein the peptide component is immobilized to said bone-compatible matrix.

34. (Original) The implant of claim 30, wherein the peptide component is impregnated or encapsulated within said bone-compatible matrix.

35. (Original) The implant of claim 30, wherein said bone-compatible matrix is selected from the group consisting of biodegradable polymer, demineralized bone matrix, ceramic and combinations thereof.

36. (Currently amended) A treatment method for promoting proliferation of osteoblasts comprising administering to a patient in need of such treatment an osteoinductive composition comprising an isolated or recombinant peptide component having the formula:



Formula (I)

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~~or a derivative~~ or a pharmaceutically acceptable salt thereof, wherein:

R₁ is H; formyl; mono- or di-lower (C1-C8 linear or branched) alkyl; aryl; lower (C1-C8 linear or branched) alkanoyl; aroyl; aroyl substituted with 1-3 substituents selected from a the group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy; C1-C8 linear or branched alkyloxycarbonyl; aryloxycarbonyl; or aryloxycarbonyl substituted with 1-3 substituents selected from a the group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy;

R₂ and R₈ are each independently selected from D-cysteine, L-cysteine, D-homocysteine, L-homocysteine, D-penicillamine, or L-penicillamine;

R₃, R₄ and R₅ are each glycine; or R₃ and R₄ taken together are δ -amino-pentanoic acid; or R₄ and R₅ taken together are δ -amino-pentanoic acid;

R₆ is arginine or homo-arginine;

R₇ is tryptophan;

R₉ is glycine; and

R₁₀ is OH, C1-C8 linear or branched alkyl ester, lower aryl ester, or NR₁₁R₁₂ where R₁₁ and R₁₂ are each selected independently from H, C1-C8 linear or branched alkyl, or aryl.

37. (Original) The method of claim 36, wherein the peptide component has the amino acid sequence of SEQ. ID NO:1.

38. (Original) The method of claim 36, wherein the composition administered comprises a homodimer of said peptide component.

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39. (Original) The method of claim 36, wherein the composition administered further comprises osteoprogenitor stem cells and/or osteoblasts.

40. (Original) The method of claim 36, wherein the composition administered further comprises a pharmaceutically acceptable carrier or aqueous solvent.

41. (Original) The method of claim 36, wherein the composition administered further comprises a delivery vehicle for said peptide component, said delivery vehicle being a bone-compatible matrix which provides for slow release of said peptide component to a patient in need of said composition.

42. (Original) The method of claim 36, wherein said bone-compatible matrix is selected from the group consisting of biodegradable polymer, demineralized bone matrix, ceramic and combinations thereof.

43. (Original) The method of claim 36, wherein the composition is administered locally as an implant or device, topically or systemically.

44. (Original) The method of claim 36, wherein the treatment is useful for treating bone fractures.

45. (Original) The method of claim 36, wherein the treatment is useful for treating diseases or anomalies associated with deficient sites of bone.

46. (Original) The method of claim 45, wherein said diseases are selected from the group consisting of rheumatoid arthritis and osteoporosis.

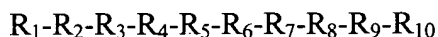
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47. (Original) The method of claim 45, wherein said anomalies are selected from the group consisting of craniofacial anomalies, dental anomalies and periodontal anomalies.

48. (Original) The method of claim 36, further comprising the step of monitoring the treatment with an antibody against the peptide component or a fragment thereof.

49. (Canceled)

50. (Currently amended) A method of preparing an osteoinductive composition comprising combining a bone-compatible matrix with a peptide component; and immobilizing said peptide component to or within said bone-compatible matrix, the peptide component having the formula:



Formula (I)

~~or a derivative~~ or a pharmaceutically acceptable salt thereof, wherein:

R₁ is H; formyl; mono- or di-lower (C1-C8 linear or branched) alkyl; aryl; lower (C1-C8 linear or branched) alkanoyl; aroyl; aroyl substituted with 1-3 substituents selected from a the group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy; C1-C8 linear or branched alkyloxycarbonyl; aryloxycarbonyl; or aryloxycarbonyl substituted with 1-3 substituents selected from a the group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy;

R₂ and R₈ are each independently selected from D-cysteine, L-cysteine, D-homocysteine, L-homocysteine, D-penicillamine, or L-penicillamine;

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R₃, R₄ and R₅ are each glycine; or R₃ and R₄ taken together are δ -amino-pentanoic acid; or R₄ and R₅ taken together are δ -amino-pentanoic acid;

R₆ is arginine or homo-arginine;

R₇ is tryptophan;

R₉ is glycine; and

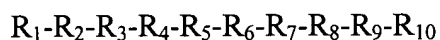
R₁₀ is OH, C1-C8 linear or branched alkyl ester, lower aryl ester, or NR₁₁R₁₂ where R₁₁ and R₁₂ are each selected independently from H, C1-C8 linear or branched alkyl, or aryl.

51. (Original) The method of claim 50, further comprising the step of combining said osteoinductive composition with osteoprogenitor stem cells and/or osteoblasts.

52. (Original) The method of claim 51, further comprising impregnating or encapsulating said cells within said bone-compatible matrix.

53. (Original) The method of claim 50, wherein the peptide component has the amino acid sequence of SEQ. ID NO:1.

54. (Currently amended) A composition comprising the reaction product of (i) a bone-compatible matrix; (ii) osteoinductive cells; and (iii) a peptide component having the formula:



Formula (I)

~~or a derivative~~ or a pharmaceutically acceptable salt thereof, wherein:

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R₁ is H; formyl; mono- or di-lower (C1-C8 linear or branched) alkyl; aryl; lower (C1-C8 linear or branched) alkanoyl; aroyl; aroyl substituted with 1-3 substituents selected from a the group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy; C1-C8 linear or branched alkyloxycarbonyl, aryloxycarbonyl or aryloxycarbonyl substituted with 1-3 substituents selected from a the group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy;

R₂ and R₈ are each independently selected from D-cysteine, L-cysteine, D-homocysteine, L-homocysteine, D-penicillamine, or L-penicillamine;

R₃, R₄ and R₅ are each glycine; or R₃ and R₄ taken together are δ -amino-pentanoic acid; or R₄ and R₅ taken together are δ -amino-pentanoic acid;

R₆ is arginine or homo-arginine;

R₇ is tryptophan;

R₉ is glycine; and

R₁₀ is OH, C1-C8 linear or branched alkyl ester, lower aryl ester, or NR₁₁R₁₂ where R₁₁ and R₁₂ are each selected independently from H, C1-C8 linear or branched alkyl, or aryl.

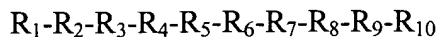
55. (Original) The composition of claim 54, wherein the peptide component has the amino acid sequence of SEQ. ID NO:1.

56. (Currently amended) A kit including one or more containers comprising:

(i) a material selected from the group consisting of (a) bone-compatible matrix, (b) carrier or aqueous solvent, (c) stabilizer, (d) preservative, (e) thickener, (f) solubilizer, and (g) cells capable of forming bone; and

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(ii) one or more containers comprising a peptide component having the formula:



Formula (I)

~~or a derivative~~ or a pharmaceutically acceptable salt thereof, wherein:

R₁ is H; formyl; mono- or di-lower (C1-C8 linear or branched) alkyl; aryl; lower (C1-C8 linear or branched) alkanoyl; aroyl; aroyl substituted with 1-3 substituents selected from ~~a the~~ group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy; C1-C8 linear or branched alkyloxycarbonyl, aryloxycarbonyl or aryloxycarbonyl substituted with 1-3 substituents selected from ~~a the~~ group consisting of fluorine, chlorine, bromine, C1-C8 linear or branched alkyl, ~~or~~ and C1-C8 linear or branched alkyloxy;

R₂ and R₈ are each independently selected from D-cysteine, L-cysteine, D-homocysteine, L-homocysteine, D-penicillamine, or L-penicillamine;

R₃, R₄ and R₅ are each glycine; or R₃ and R₄ taken together are δ-amino-pentanoic acid; or R₄ and R₅ taken together are δ-amino-pentanoic acid;

R₆ is arginine or homo-arginine;

R₇ is tryptophan;

R₉ is glycine; and

R₁₀ is OH, C1-C8 linear or branched alkyl ester, lower aryl ester, or NR₁₁R₁₂ where R₁₁ and R₁₂ are each selected independently from H, C1-C8 linear or branched alkyl, or aryl.

57. (Original) The kit of claim 56, wherein the peptide component has the amino acid sequence of SEQ. ID NO:1.

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58. (Withdrawn) An isolated DNA sequence encoding the peptide of SEQ. ID NO:1.

59. (Original) An isolated or recombinant peptide having SEQ. ID NO: 1.

60. (New) The implant of claim 30, wherein the peptide component is part of a longer peptide or polypeptide.

61. (New) The method of claim 36, wherein the peptide component is part of a longer peptide or polypeptide.

62. (New) The method of claim 50, wherein the peptide component is part of a longer peptide or polypeptide.

63. (New) The composition of claim 54, wherein the peptide component is part of a longer peptide or polypeptide.

64. (New) The kit of claim 56, wherein the peptide component is part of a longer peptide or polypeptide.